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Papillary Thyroid Carcinoma: Demographics, Treatment, and Outcome in Eleven Pediatric Patients Treated at a Single Institution

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We describe 11 cases (8 females, 3 males) of papillary thyroid carcinoma in children treated at St. Jude Children's Research Hospital over a 33-year period, and review the literature. Ages ranged from 7–25 years (median, 16 years). Six patients had primary papillary thyroid carcinoma. Five patients had secondary papillary thyroid carcinoma after treatment of Hodgkin's disease (n = 2), acute lymphoblastic leukemia (n = 2), and neuroblastoma (n = 1) with chemotherapy and cervical radiation. The typical presentation was either cervical lymphadenopathy or a thyroid mass of short duration. Treatment consisted of thyroidectomy, cervical lymph node dissection, and postoperative thyroid hormone replacement (n = 11), parathyroid reimplantation (n = 1), ^{131}I ablation (n = 4),external-beam irradiation (n = 1), and chemotherapy with doxorubicin (n = 1) or carboplatin and topotecan (n = 1). Nine patients are alive without evidence of disease 3.0–22.4 years from diagnosis. One patient has persistent but stable disease 17.3 years after diagnosis. One patient relapsed with metastatic lung disease 0.8 years after the initial diagnosis. He continues to do well after a brief but unsustained complete radiographic remission of disease to combination chemotherapy with carboplatin and topotecan. Our review supports excellent long-term outcome for primary or secondary papillary thyroid carcinoma in pediatric patients, although complications may require close follow-up in a multidisciplinary setting. Med. Pediatr. Oncol. 28:433–440, 1997.

Key words: papillary carcinoma; thyroid gland; pediatrics; carboplatin; topotecan

INTRODUCTION

Thyroid carcinomas are rare tumors in childhood and adolescence. The incidence ranges from 0.2–5 per million per year [1], 85–90% of which are of the papillary type histologically. A rapid rise occurs after the age of 5 [2]. Patients most commonly present with anterior cervical adenopathy of long duration. Other presentations include a firm, palpable thyroid nodule with or without enlarged cervical lymph nodes. In more than 50% of cases, papillary thyroid carcinoma spreads to local, cervical, and upper mediastinal lymph nodes, but this does not necessarily worsen the prognosis. Lung metastases occur in 20% of children with papillary thyroid carcinoma, whereas bone metastases or metastases to sites below the diaphragm are uncommon [3–6]. Patients are usually euthyroid at diagnosis.

Surgery and radioiodine are the mainstays of treatment. With such treatment, the prognosis for most pediatric patients is excellent. A series with 30 years of follow-up demonstrates death from papillary thyroid cancer between 1% for adults and 4% for children under 17 years of age (24% for less than 11 years of age); mortality may be somewhat higher (11%) in adults 40 years of age or older [1].

Experience with chemotherapy or external-beam radiation for metastatic differentiated thyroid carcinoma has been generally disappointing [7–12]. Doxorubicin and bleomycin have been studied most intensively, and many other single agents and combinations have been tried. Response rates between 9% and 64% have been reported [13–15].

We offer an analysis of 11 consecutive pediatric patients with papillary thyroid carcinoma treated at St. Jude Children's Research Hospital with an emphasis on presentation, treatment, outcome, and complications. Additionally, we note one patient who achieved a complete radiographic resolution of lung metastases for 2 months

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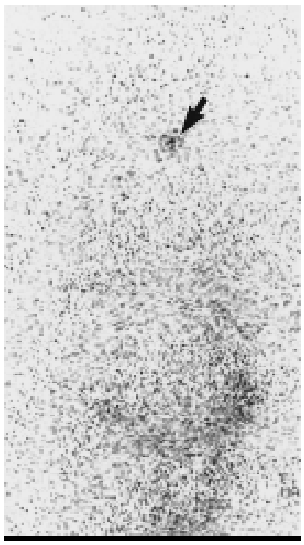

Fig. 1. The postoperative, pre-treatment ^{131}I scan shows uptake in the neck area (arrow).

with a novel phase I combination chemotherapy regimen with carboplatin and topotecan.

MATERIALS AND METHODS

Eleven consecutive pediatric patients with papillary thyroid carcinoma treated at St. Jude Children's Research Hospital between 1962 and 1995 were identified by chart review. Histopathologic material was reviewed in each case by one author (J.J.J.) to confirm the diagnosis of papillary thyroid carcinoma. Detailed information regarding presentation, treatment, and response has been summarized in tables IA, IB, IIA, and IIB.

Case Report

A 7-year-old black male (patient 6) presented with a 4-year history of cervical lymphadenopathy. Initial thyroid function studies were normal with the exception of a slightly elevated thyroglobulin (73 ng/mL; normal for prepubertal children 4–55 ng/mL, mean 22 ng/mL). Computed tomography (CT) scan of the neck and chest showed cervical metastases, but no pulmonary metastases. The patient underwent near-total thyroidectomy, cervical lymph node dissection, bilateral neck dissection, and reimplantation of parathyroid tissue in the left sternocleidomastoid muscle. Thyroid tissue of 1 cm in diameter infiltrating the right tracheal wall could not be removed.

Oral supplementation with calcium and vitamin D was given as clinically indicated. Two months after surgery, a markedly elevated thyroglobulin level (960 ng/mL) suggested persistence of residual thyroid tissue, which was confirmed by a diagnostic ^{131}I scan (300 μCi) showing faint uptake in the region of the thyroid bed (Fig. 1). He was treated with an adjuvant dose of ^{131}I (28.4 mCi). Within 7 weeks thyroglobulin had dropped to 59 ng/mL, and thyroxine suppression therapy was started, which further decreased TSH levels below 0.1 μU/mL (normal 0.5–4.8 μU/mL, mean 1.6 μU/mL). A high-resolution CT of the chest on routine follow-up 7 months after thyroidectomy demonstrated multiple new pulmonary lesions suggesting metastases (Fig. 2B). A chest x-ray showed normal lung fields, but narrowing of the cervical trachea. A ^{131}I scan showed no lung uptake. Thyroglobulin had increased to 92 ng/mL, while TSH remained below 0.1 μU/mL. A technetium-99m-sestamibi (Cardiolite®) scan showed abnormal uptake in the upper lobes of the lung, confirming the occurrence of metastases (Fig. 2A).

He began a phase I chemotherapy regimen with carboplatin and topotecan. The carboplatin dose was calculated using the formula Dose (mg/m^2) = 6.5 × (0.93 GFR + 15) to achieve a targeted area under the curve of 6.5 mg/mL/hr. Carboplatin was administered intravenously over 1 hour on day 1 of chemotherapy. Topotecan (0.6 mg/m^2/day) was given as a continuous intravenous infusion over 72 hours. Cycles were repeated every 21 days or as soon thereafter as the absolute neutrophil count was $\geq$1,000/mm^3 and the platelet count was $\geq$100,000/mm^3. Because of severe and prolonged neutropenia, granulocyte colony-stimulating factor (G-CSF) was added at a dose of 5 μg/kg for 10–14 days for cycles 2–6. After 4 courses of carboplatin and topotecan, the patient achieved a complete radiographic disappearance of disease with a normal ^{99m}Tc-sestamibi scan (Fig. 3A) and chest CT (Fig. 3B), and the thyroglobulin had dropped to 33 ng/mL with a TSH of 0.01 μU/mL. After chemotherapy course 6, a ^{99m}Tc-sestamibi scan demonstrated disease progression with increased pulmonary uptake (Fig. 4A). A high-resolution chest CT showed several new micronodules (Fig. 4B), and chemotherapy was discontinued. He continues to be asymptomatic and has been managed with thyroid suppression only. Thyroglobulin remained normal with a level of 26 ng/mL two months after chemotherapy cessation. Both a chest CT 3 months and a ^{99m}Tc-sestamibi scan 4 months after discontinuation of chemotherapy showed stable disease.

RESULTS

Tables IA and IB describe the demographics and presentation of the 11 patients. Six patients had primary papillary thyroid carcinoma, and 5 developed papillary thyroid carcinoma as a secondary neoplasm after chemotherapy and irradiation of the cervical area for Hodgkin's disease (patients 7, 9), acute lymphoblastic leukemia (patients 8, 10), and neuroblastoma (patient 11). The latency between initial diagnosis and subsequent irradiation of the neck and the diagnosis of thyroid cancer was a median of 11.4 years (range 9.2–18.9 years). Physical findings at presentation included cervical adenopathy in 4, a

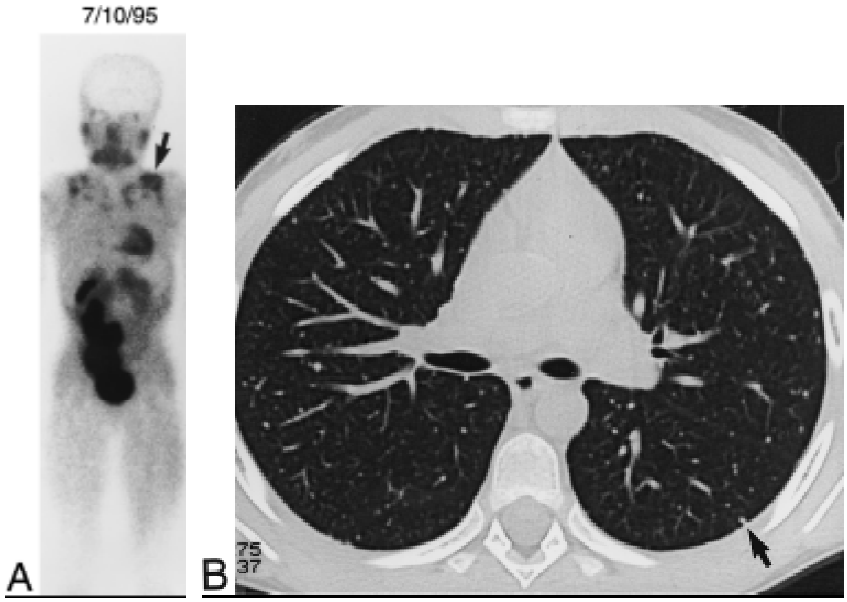

Fig. 2. (A) ^{99m}Tc-sestamibi scan at first relapse showing uptake in the lung (arrow). **(B)** High-resolution chest CT at first relapse showing lung metastases (arrow).

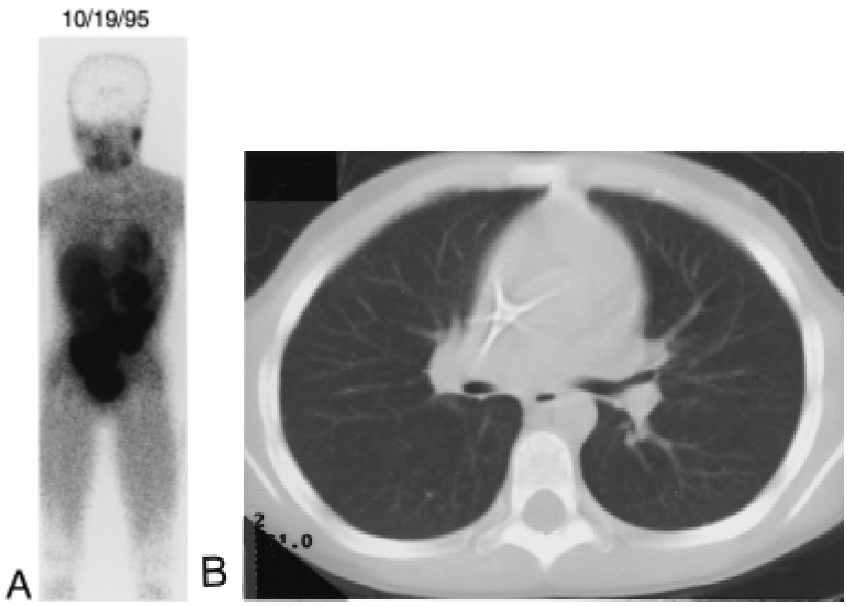

Fig. 3. (A) ^{99m}Tc-sestamibi scan at radiographic remission. **(B)** Chest CT at radiographic remission.

single thyroid nodule in 4, and a combination of cervical adenopathy and thyroid nodules in 3 patients. Two patients had unusual presentations: patient 4 developed acute respiratory distress after a motor-cycle accident, and patient 6 had cervical lymphadenopathy for 4 years. In 9 patients, signs of disease had been present for less than 6 weeks prior to diagnosis. Patients 7 and 11 had no metastases. Nine patients had cervical metastases, and in 4, the superior mediastinum was also involved.

Tables IIA and IIB describe treatment and outcome. Four patients were treated with hemithyroidectomy, 6 with subtotal thyroidectomy with or without neck dissection, and one with near-total thyroidectomy, bilateral cervical lymph node dissection, and reimplantation of parathyroid tissue. One patient received external-beam radiation therapy, 4 were treated with radioiodine, and two had chemotherapy.

Complications included hypoparathyroidism after surgery in two patients (patients 6, 8). Patient 4 required a tracheostomy and mechanical ventilation at diagnosis. All patients are alive with a median follow-up of 14.2 years (range 1.3–22.4 years). Nine patients are free of tumor at a median of 14.2 years (range 3.0–22.4 years). Two patients (patients 4, 6) have persistent but stable lung metastases.

DISCUSSION

The etiology of primary thyroid carcinoma is unknown. A novel rearranged form of the *ret* proto-

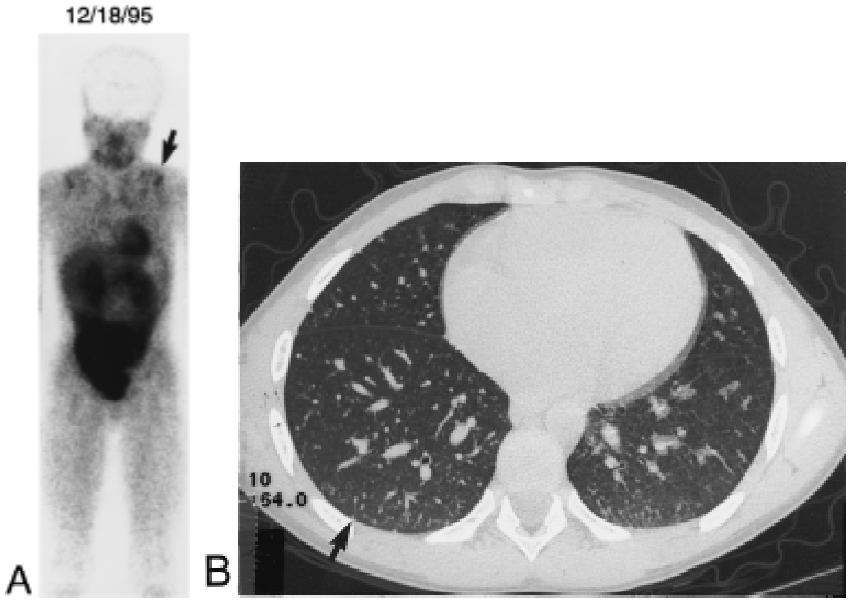

Fig. 4. (A) ^{99m}Tc-sestamibi scan at second relapse showing uptake in the lung (arrow). **(B)** High-resolution chest CT at second relapse showing lung metastases (arrow).

TABLE IA. Characteristics of Patients With Primary Papillary Thyroid Carcinoma at Diagnosis

Patient no.	Age (year)/sex	Physical finding	Metastases at diagnosis
1	11/F	Cervical lymph node	Cervical nodes, superior mediastinum
2	7/F	Cervical lymph node	Cervical nodes, trachea, superior mediastinum
3	16/F	Thyroid mass	None
4	14/M	Acute respiratory distress, cervical lymph nodes	Cervical nodes, trachea, superior mediastinum, lungs, bone
5	16/F	Cervical lymph node	Cervical nodes
6	7/M	Several cervical lymph nodes	Cervical nodes, trachea, superior mediastinum

TABLE IB. Characteristics of Patients With Secondary Papillary Thyroid Carcinoma at Diagnosis

Patient no.	Age (year)/sex	Presentation/Primary diagnosis	Metastases at diagnosis	Radiation dose (Gy/volume)	Latency (year)
7	19/M	Thyroid mass/Hodgkin's disease stage IVB	None	33/cervical nodes, mediastinum 15/lung fields	9.2
8	19/F	Cervical lymph node, thyroid mass/Acute lymphoblastic leukemia	Cervical nodes	24/cranium 23.6/spine	14.3
9	25/F	Cervical lymph node, thyroid mass/Hodgkin's disease stage IIIA	Cervical nodes	20/mantle, periaortic	11.3
10	19/F	Thyroid mass/Acute lymphoblastic leukemia	Cervical nodes	24/cranium	11.4
11	20/F	Thyroid mass/Neuroblastoma stage IIB in right superior sympathetic ganglion	None	22/right superior sympathetic ganglion	18.9

oncogene termed PTC (for papillary thyroid carcinoma) is frequently detected *in vivo* in human papillary thyroid carcinomas [16]. Although rare disorders have been described in association with papillary thyroid carcinoma, including carotid body tumors, Gardner's and Pendred's syndromes [17], and autoimmune thyroid disease [18], none of these were seen in our patients.

One of the most common associations is that of radiation-induced malignant transformation of the thyroid gland. Patients treated for benign conditions as well as malignant diseases have been reported to develop papillary thyroid carcinoma after prior irradiation of the thyroid [19,20]. Secondary thyroid carcinomas after chemotherapy and radiation therapy including the thyroid gland for Hodgkin's disease and other tumors in children have been well documented in several studies. Among children treated for Hodgkin's disease, the risk of subsequent thyroid cancer is increased 68-fold [21], compared with a 16-fold increase in a predominantly adult group (average age, 28 years) treated during an equivalent time period [22]. Thyroid malignancies have been reported to appear as early as 3-5 years after radiation exposure, with a peak incidence between 15 and 25 years [23–25].

Thyroid neoplasms after craniospinal radiotherapy for

TABLE IIA. Treatment and Outcome of Patients With Primary Papillary Thyroid Carcinoma

Patient no.	Initial surgery	Further therapy	Progression	Survival after diagnosis (years)
1	Subtotal thyroidectomy + left radical neck dissection	External radiation therapy neck and superior mediastinum (4650 cGy)	None	22.4
2	Subtotal thyroidectomy + partial thymectomy	3 × ^{131}I (30 mCi)	None	17.9
3	Total right thyroid lobectomy		None	16.8
4	Subtotal thyroidectomy + partial thymectomy	1 × adriamycin prior to surgery (60 mg/m^2)	Stable disease (lung metastases)	17.3
5	Subtotal thyroidectomy	1 × ^{131}I (51 mCi)	None	14.2
6	Near-total thyroidectomy with neck dissection	1 × ^{131}I (28.4 mCi) 6 × carboplatin and topotecan	Lung metastases 0.8 years after diagnosis	1.3

TABLE IIB. Treatment and Outcome of Patients With Secondary Papillary Thyroid Carcinoma

Patient no.	Initial surgery	Further therapy	Progression	Survival after diagnosis (years)
7	Total left thyroid lobectomy		None	15.0
8	Subtotal thyroidectomy + modified radical neck dissection	2 × ^{131}I	None	10.4
9	Total right thyroid lobectomy + modified right neck dissection		None	4.9
10	Subtotal thyroidectomy + lymph node excision		None	4.9
11	Completion thyroidectomy		None	3.0

acute lymphoblastic leukemia are also seen. In a retrospective cohort study of 9720 children with a median follow-up of 4.7 years, 3 patients developed thyroid cancers [26]. With longer follow-up, the risk increases dramatically, from not significantly elevated at less than 5 years to a 100-fold increased risk at 20 years [27].

A study at the Mayo Clinic found that children and adolescents with papillary thyroid carcinoma tend to present with more advanced disease than adults [28]. Diagnosis might be delayed because cervical lymphadenopathy is common in children and is usually due to other causes. Children had larger tumors, a higher incidence of neck node and distant metastases, as well as recurrence of neck node metastases. However, despite the relatively advanced disease in children, the course of the disease is indolent, and younger age at presentation is an important predictor of a good outcome [1,29].

The rarity of the tumor and the excellent outcome with several forms of therapy have made randomized studies difficult. The extent of surgical removal of the thyroid gland is a controversial issue. The benefits of total vs. partial thyroidectomy are a matter of debate. Several reasons argue for the removal of as much thyroid tissue as possible, as: (1) 20%–30% of the cancers are multifocal and remaining thyroid tissue might contain cancer; (2) residual thyroid tissue provides a source of thyroglobulin that diminishes the specificity of thyroglobulin postoperatively as a tumor marker; (3) remaining thyroid tissue might interfere with the use of radioiodine for postoperative diagnostic scanning and treatment of microscopic regional and distant disease. These considerations suggest that aggressive surgery with total or near-total thyroidectomy is the best course. Regional control of thyroid cancer appears to be extremely important in preventing recurrences [30]. A modified neck dissection on the side of the primary tumor is indicated, with possible extension to the contralateral side if involvement is found at surgery. Bilateral surgical procedures substantially decreased tumor recurrence in children, as compared to recurrence after unilateral procedures [1]. This approach is supported by data from a large prospective study of adults with well-differentiated thyroid cancer [31]. Those who favor subtotal thyroidectomy argue that total thyroidectomy has a potentially increased complication rate, with injury to the recurrent laryngeal nerve and permanent hypoparathyroidism, and that more aggressive surgery does not necessarily improve outcome; however, there is no advantage to leaving a thyroid remnant to avoid hypothyroidism, since all these patients go on to suppressive L-thyroxine therapy.

The administration of radioiodine for ablation of thyroid remnants, usually 6 weeks after total thyroidectomy, is supported by retrospective analyses showing a decreased rate of recurrences in adults [29,32–34]. Nevertheless, a study of 45 children untreated with ^{131}I failed to show a relationship between ^{131}I ablation of thyroid remnants and post-treatment tumor recurrence [1]. The adverse effects and complications of acute and subacute radioiodine therapy include transient radiation sickness, acute or chronic sialoadenitis, leukopenia or thrombocytopenia, and transient oligospermia or azoospermia [35]. It is unclear whether an increased incidence of malignan-

cies is a long-term complication of radioiodine therapy [35–38].

Thyroid hormone suppression is indicated to keep serum TSH at the lower assay limit and thereby prevent stimulation of tumor regrowth and to suppress thyroglobulin levels to increase the sensitivity of this test for recurrence screening. Hormonal agents are generally palliative but not tumoricidal [39]. Conclusive data about the efficiency of thyroid suppression in patients is lacking [40].

The prognosis and optimal care of children with differentiated thyroid cancer and pulmonary metastases are not well established [3,6,41–43]. Pulmonary metastases occur in 6–20% of children and young adults, and are almost always diffuse and responsive to ^{131}I therapy [3]. The chest x-ray may be normal in almost half of the patients [3]. Pulmonary metastases may be overlooked unless near-total thyroidectomy is followed by total body radioiodine scan in all children and young adults who have regional lymphadenopathy of the neck. Although ^{131}I therapy is efficacious in clearing radiographic abnormalities on chest x-ray, it may not eradicate the metastatic foci in many patients [3].

Previous experience with other treatments for metastatic differentiated thyroid cancer, such as chemotherapy or external-beam irradiation, has been disappointing. Chemotherapy has been given for progressive, symptomatic recurrent, or metastatic thyroid cancer unresponsive to conventional treatment [13–15]. Carboplatin is one of many drugs tried previously, and 2 of 9 patients responded in one series [15]. This agent, a heavy-metal coordination complex, has been successfully used against a variety of pediatric solid tumors both as a single agent [44–47] and in combination therapy [48–51]. Topotecan, a water-soluble camptothecin derivative, is a topoisomerase-I inhibitor and has shown promising activity in preclinical and phase I studies [52–55]. Although results from phase II studies of this agent are pending, evidence of activity was noted in phase I trials in adults with carcinomas and acute leukemias [54,56,57] as well as in pediatric solid tumors such as rhabdomyosarcoma, neuroblastoma, and medulloblastoma [58]. *In vitro* studies of combinations of topoisomerase-I inhibitors and platinating agents have demonstrated at least additive cytotoxicity [59].

Patient 6 was enrolled in an institutional phase I evaluation of topotecan and carboplatin combination chemotherapy in pediatric malignancies. Although the activity of these agents in childhood thyroid carcinoma is not known, they have produced responses in a variety of other childhood tumors. We are encouraged that this novel combination showed excellent activity in a case of papillary thyroid carcinoma, producing a complete radiographic resolution of disease with recurrence within 2 months while on triiodothyronine suppression therapy.

Our experience in this small group of patients suggests that thyroid carcinoma should be followed indefinitely by a combination of regular examinations, non-contrast CT scans of the chest, nuclear scans with ^{99m}Tc-sestamibi or ^{131}I, thyroid hormone studies, and thyroglobulin levels. The contribution of chemotherapy in addition to surgery and ^{131}I requires further study.

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